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EXAMINER	
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ART UNIT	PAPER NUMBER
1645	

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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/054,638	RYALL, ROBERT P.	
	Examiner	Art Unit	
	S. Devi, Ph.D.	1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09/08/04*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18-57* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *18-57* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *070704*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Request for Continued Examination

1) A request for continued examination under 37 C.F.R 1.114, including the fee set forth in 37 C.F.R 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R 1.114, and the fee set forth in 37 C.F.R 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R 1.114. Applicants' submission filed on 07/07/04 has been entered.

Applicant's Amendment

2) Acknowledgment is made of Applicant's amendment filed 09/08/04 in response to the final Office Action mailed 01/07/04.

Status of Claims

3) Claims 1-17 have been canceled via the amendment filed 10/14/03.

Claims 18-33 have been amended via the amendment filed 09/08/04.

New claims 34-57 have been added via the amendment filed 09/08/04.

Claims 18-57 are pending and are under examination.

Information Disclosure Statement

4) Acknowledgment is made of Applicants' Information Disclosure Statement filed 07/07/04. The information referred to therein has been considered and a signed copy is attached to this Office Action. The references that have already been cited and/or considered previously have been lined through.

Prior Citation of Title 35 Sections

5) The text of those sections of Title 35 U.S. Code not included in this action can be found in a prior Office Action.

Prior Citation of References

6) The references cited or used as prior art in support of one or more rejections in the instant Office Action and not included on an attached form PTO-892 or form PTO-1449 have been previously cited and made of record.

Objection(s) Withdrawn

7) The objection to claim 18 made in paragraph 17 of the Office Action mailed 01/07/04 is withdrawn in light of Applicant's amendment to the claim.

Rejection(s) Withdrawn

8) The rejection claims 22-32 made in paragraph 13 of the Office Action mailed 01/07/04 under 35 U.S.C. § 112, first paragraph, as containing new subject matter, is withdrawn in light of upon further consideration.

9) The rejection claim 18 made in paragraph 14(a) of the Office Action mailed 01/07/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.

10) The rejection claims 19-29 and 33 made in paragraph 14(c) of the Office Action mailed 01/07/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claims.

11) The rejection claim 29 made in paragraph 14(d) of the Office Action mailed 01/07/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claim.

12) The rejection claims 30-32 made in paragraph 14(e) of the Office Action mailed 01/07/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is withdrawn in light of Applicant's amendment to the claims.

13) The rejection claims 18-33 made in paragraph 16 of the Office Action mailed 01/07/04 under 35 U.S.C. § 103(a) as being unpatentable over Granoff (WO 98/58670 - already of record) ('670) or Ambrosch *et al.* (*Bull WHO* 61 (2): 317-323, 1983) in view of Andre *et al.* (*In*: *Modern Vaccinology*. (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, pp. 41-54, 1994), and Levine *et al.* (*In*: *Abstracts of the Tenth International Pathogenic Neisseria Conference*, (Ed) Zollinger *et al.* Baltimore, USA, pages 228-230, November, 1997), is withdrawn upon further consideration.

Rejection(s) Maintained

14) The rejection claim 18 made in paragraph 14(b) of the Office Action mailed 01/07/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for reasons set forth therein. It is suggested that Applicants delete the limitation 'derived' since it is unnecessary.

15) The rejection claims 19-33 made in paragraph 14(f) of the Office Action mailed 01/07/04 under 35 U.S.C. § 112, second paragraph, as being indefinite, is maintained for reasons set forth

therein.

New claims 34-57, which depend directly or indirectly form claim 18, are also rejected as being indefinite because of the indefiniteness identified above in the base claim.

16) The rejection claims 18-33 made in paragraph 15 of the Office Action mailed 01/07/04 are rejected under 35 U.S.C. § 102(b) as being anticipated by Chong *et al.* (WO 99/42130), is maintained for reasons set forth therein and herebelow.

Applicant cites case law and contends that a claim is anticipated only if each and every element as set forth in the claim is found, whether expressly or inherently described, in a single prior art reference. Applicant asserts that the '130 publication doe not teach each and every element of the instantly claimed invention. Applicant acknowledges that the '130 publication is directed to multivalent immunogenic conjugate molecules comprising a single carrier protein conjugated to multiple, distinct capsular bacterial polysaccharides or tumor antigens, and that the polysaccharides may be selected from different serogroups of a single species of bacteria and/or from one or more distinct bacterial species. Applicant submits that the instantly claimed compositions relate to distinct polysaccharide-carrier conjugates, e.g., A-carrier, Y-carrier, W-135-carrier, C-carrier, which are 'individually prepared and subsequently combined' to provide multivalent immunogenic compositions, e.g., 'combinations' of A-carrier, C-carrier, Y-carrier and/or W-135 carrier. Applicant cites various parts of the '130 publication and states that the publication describes a multivalent immunogenic molecule comprising 'a carrier molecule' and multiple different carbohydrate fragments 'each linked to the carrier molecule'. Applicant maintains that the '130 publication is completely silent about individual immunoconjugates used in combination with one another. With regard to Chong's Figure 9, Applicant states that Figure 9 relates to the immunogenicity of a meningococcal multivalent immunogenic conjugate, because lines 28-31 on page 23 describe Figure 9 to be showing that the meningococcal glycoconjugate could elicit antibody responses to all three polysaccharides.

Applicant's arguments have been carefully considered, but are not persuasive. Contrary to Applicant's assertion, the claimed product is not claimed as a 'combination' product comprising 'individual' immunoconjugates, wherein each capsular polysaccharide is '*separately conjugated*' to a carrier protein. In other words, as claimed currently, two, three or four protein-capsular

polysaccharide conjugates are not a combination of isolated conjugates, and are not required to comprise the recited purified meningococcal capsular polysaccharide(s) '*conjugated separately*' to a carrier protein. Therefore, instant claims are anticipated by Chong's disclosure. As set forth previously and as acknowledged by the Applicant, Chong's multivalent immunogenic conjugate molecules comprise a carrier protein as recited in the instant independent claim, wherein the carrier protein is conjugated to at least two distinct capsular bacterial polysaccharides from different serogroups of a single species of bacterium, *N. meningitidis*. Chong's meningococcal multivalent immunogenic conjugates, being distinct by way of capsular polysaccharides, are not excluded from the scope of the instant claims, as presented currently. The rejection stands.

Rejection(s) under 35 U.S.C. § 112, First Paragraph (New Matter)

17) Claims 52-55 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claim 52 includes the limitations: 'sterile liquid is contained within in a single use syringe'. New claim 53 includes the limitations: 'syringe is packaged in a box with instructions for administration of said composition'. New claim 54 includes the limitations: 'sterile liquid is contained within a vial'. New claim 55 includes the limitations: 'vial is packaged in a box with instructions for administration of said composition'. However, there is no descriptive support in the specification, as originally filed for the above-identified new limitations. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicant is respectfully requested to remove the new matter from the claim(s), or invited to point to specific pages and line numbers in the originally filed specification where support for such recitations can be found.

18) Claims 38-45 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one

skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claims 38, 40, 42 and 44 include the limitations: 'from about 0.02 μg to about 5 μg of said purified *N. meningitidis* capsular polysaccharide ... conjugated to about 30 to 60 μg of carrier protein'. New claims 39, 41, 43 and 45 include the limitations: '4 μg of purified *N. meningitidis* capsular polysaccharide ... conjugated to about 48 μg of carrier protein'. However, there is no descriptive support in the specification, as originally filed for the above-identified new limitations and/or ranges. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicant is respectfully requested to remove the new matter from the claim(s), or invited to point to specific pages and line numbers in the originally filed specification where support for such recitations can be found.

19) Claims 47 and 48 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor, at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

New claim 47 includes the limitations: 'said carrier protein species comprises an inactivated bacterial toxin'. The term 'inactivated bacterial toxin' encompassed within its scope any inactivated toxin from any bacterium. However, the specification as originally filed does not appear to provide support for an inactivated bacterial toxin of such a broad scope. The description in first three lines of section [0027] of the specification is limited to carrier proteins that include inactivated bacterial toxins 'such as diphtheria toxoid, CMR197, tetanus toxoid, pertussis toxoid, *E. coli* LT, *E. coli* ST, and exotoxin A from *Pseudomonas aeruginosa*'.

New claim 48, which depends from claim 47, includes the limitations: said inactivated bacterial toxin is derived from an 'organism' selected from the group consisting of *Corynebacterium diphtheriae, Clostridium tetani, Bordetella pertussis, Pseudomonas aeruginosa,*

and *Escherichia coli*. The term 'organism' encompasses those other than bacteria, such as, fungi, parasites etc. However, there appears to be no descriptive support in the instant specification, as originally filed, for an inactivated bacterial toxin 'derived from an organism', as recited in claim 48. Furthermore, other than tetanus toxoid from *Clostridium tetani*, diphtheria toxoid and CRM197 from *Corynebacterium diphtheriae,* pertussis toxoid from *Bordetella pertussis*, exotoxin A from *Pseudomonas aeruginosa*, LT and ST from *Escherichia coli*, no other inactivated toxoids from these bacteria are described in the specification, as originally filed. See lines 9-11 on page 5. For instance, *Bordetella pertussis* produces several toxins other than pertussis toxin (PT or LPF), such as, endotoxin (LPS), adenylate cyclase toxin, heat-labile toxin, tracheal cytotoxin, dermonecrotic toxin, and haemolytic toxin etc. However, inactivated forms of such toxins of such a broad scope are not supported in the instant specification. Therefore, the above-identified limitations in the claims are considered to be new matter. *In re Rasmussen*, 650 F2d 1212 (CCPA, 1981). New matter includes not only the addition of wholly unsupported subject matter but also, adding specific percentages or compounds after a broader original disclosure, or even omission of a step from a method. See M.P.E.P 608.04 to 608.04(c).

Applicant is respectfully requested to remove the new matter from the claim(s), or invited to point to specific pages and line numbers in the originally filed specification where support for such recitations can be found.

Rejection(s) under 35 U.S.C. § 112, Second Paragraph

20) Claims 18-57 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite, for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention.

(a) Claim 18 is incorrect and/or confusing in the recitations: 'capsular polysaccharide derived from a serogroup of *N. meningitidis* ..... wherein at least one serogroup is W-135 or Y', because the capsular polysaccharide can be obtained from *N. meningitidis* of a sergroup, but cannot be from a serogroup of *N. meningitidis*. For the purpose of distinctly claiming the subject matter, it is suggested that Applicant replace the above-identified phrase with: --capsular polysaccharide from *N. meningitidis* of serogroup W-135 or Y conjugated to a carrier protein--.

(b) Similarly for clarity, in claims 19-21 and 23-25, it is suggested that the limitation

'from *N. meningitidis* serogroup ..' be replaced with --from *N. meningitidis* of serogroup ...--.

(c) Claim 52 is vague, indefinite and/or incorrect in the recitation 'contained within in'.

(d) Claims 18, 26, 29 and 33 are confusing and inconsistent in the limitations: 'protein-polysaccharide conjugates, wherein each of the conjugates comprises a purified capsular polysaccharide', because the earlier recitation 'polysaccharide' is of broader scope which includes a polysaccharide other than a capsular polysaccharide within its scope, such as, a lipopolysaccharide. To be of same scope, it is suggested that Applicant replace the recitations with --protein-capsular polysaccharide conjugates, wherein each of the conjugates comprises a purified capsular polysaccharide--.

(e) Claims 20 and 21 lack proper antecedent basis in the limitation: 'at least one of the capsular polysaccharides'. Claims 20 and 21 depend from claim 19 which already includes the limitation. It is suggested that Applicant provide proper antecedence by replacing the recitation with --said at least one of the capsular polysaccharides--.

(f) Claim 22 contains incorrect Markush claim language: 'capsular polysaccharide selected from the group consisting of *N. meningitidis* serogroups Y, A **or** C' [Emphasis added]. When materials recited in a claim are so related as to constitute a proper Markush group, they may be recited in the conventional manner, or alternatively. For example, while 'wherein R is a material selected from the group consisting of A, B, C **and** D' is a proper limitation, 'wherein R is a material selected from the group consisting of A, B, C or D' is an improper limitation. It is suggested that Applicant replace the phrase with --capsular polysaccharide from *N. meningitidis* of serogroup Y, A or C--.

(g) Claims 27-32 are incorrect and/or confusing in the recitation: 'capsular polysaccharide of *N. meningitidis* serogroup ....'. For clarity and for the purpose of distinctly claiming the subject matter, it is suggested that Applicant replace the above-identified limitation with: --capsular polysaccharide from *N. meningitidis* of serogroup ....--.

(h) Analogous criticism applies to claim 26. Claim 26 is further indefinite and/or incorrect in the limitation: 'serogroups A or C' (see last line). To obviate the rejection, it is suggested that Applicant replace the limitation with: --of serogroup A or C--.

(i) Claim 26 lacks proper antecedent basis in the limitation: 'two distinct .....

conjugates'. Claim 26 depends from claim 18, which already includes the limitation. For proper antecedence, it is suggested that Applicant replace the limitation with --said two distinct ..... conjugates--.

(j) Claim 29 lacks proper antecedent basis in the limitation: 'three distinct ..... conjugates'. Claim 26 depends from claim 18, which already includes the limitation. For proper antecedence, it is suggested that Applicant replace the limitation with --said three distinct ..... conjugates--.

(k) Claim 33 lacks proper antecedent basis in the limitation: 'four distinct ..... conjugates'. Claim 26 depends from claim 18, which already includes the limitation. For proper antecedence, it is suggested that Applicant replace the limitation with --said four distinct ..... conjugates--.

(l) Claim 26 fails to distinctly claim the subject matter in the limitation: 'a first conjugate ..... a second conjugate' as opposed to the limitation --the first conjugate ..... the second conjugate--. Amendment to the claim is suggested.

(m) Claim 29 fails to distinctly claim the subject matter in the limitation: 'a first conjugate ..... a second conjugate ..... a third conjugate', as opposed to the limitation --the first conjugate ..... the second conjugate ..... the third conjugate--. Amendment to the claim is suggested.

(n) Claim 33 fails to distinctly claim the subject matter in the limitation: 'a first conjugate ..... a second conjugate ..... a third conjugate ..... a fourth conjugate', as opposed to the limitation --the first conjugate ..... the second conjugate ..... the third conjugate ..... the fourth conjugate--. Amendment to the claim is suggested.

(o) Claim 35 is vague and indefinite in the use of abbreviations in the claim language: 'pcpp', 'DC-chol', 'CpG' and 'BAY', because it is unclear what exactly is encompassed in these abbreviations. It is suggested that each abbreviation be recited as a full terminology at first occurrence in the claim, with its abbreviated recitation retained in parentheses.

(p) Claim 35 appears to include a trademark recitation: 'BAY' which renders the claim indefinite. Where a trademark or trade name is used in a claim as a limitation to identify or describe a particular material or product, the claim does not comply with the requirements of 35 U.S.C. 112,

second paragraph. See *Ex parte Simpson, 218 USPQ 1020 (Bd. App. 1982)*. The scope of the claim is uncertain since the trademark or trade name cannot be used properly to identify any particular material or product. A trademark or trade name is used to identify a source of goods, and not the goods themselves. Thus, a trademark or trade name does not identify or describe the goods associated with the trademark or trade name.

(q) Claims 36 and 37 have improper antecedence in the limitation: 'said aluminum adjuvant'. Claims 36 and 37 depend from claim 35 which includes the limitation: 'aluminum adjuvants' and not 'aluminum adjuvant'. To obviate the rejection, it is suggested that Applicant replace the limitation 'aluminum adjuvants' in claim 35 with the limitation --aluminum adjuvant--.

(r) Dependent claims 39, 41, 43 and 45 lack antecedent basis in the limitation: 'purified .... capsular polysaccharide' (see line 1). Claim 18, from which these claims depend indirectly, already recited the term 'carrier protein'. For proper antecedence, it is suggested that Applicant replace the limitation with --said purified .... capsular polysaccharide--.

(s) Dependent claims 38-45 lack antecedent basis in the limitation: 'carrier protein' (see last line). Claim 18, from which these claims depend indirectly, already recited the term 'carrier protein'. For proper antecedence, it is suggested that Applicant replace the limitation with --the carrier protein--.

(t) Claims 18 and 48-50 are vague and indefinite in the recitation: 'derived from', because it is unclear what is encompassed in the limitation 'derived'. Does 'derived' mean isolated, separated, extracted, or recombinantly expressed? It is suggested that Applicant delete the limitation 'derived' since it is unnecessary.

(u) Claim 48 is vague and indefinite in the limitation: 'said inactivated bacterial toxin is derived from an organism selected from the group consisting of *Corynebacterium diphtheriae*, *Clostridium tetani*, *Bordetella pertussis*, *Pseudomonas aeruginosa*, and *Escherichia coli*'. Each Markush species recited is a bacterium as opposed to an 'organism'. The term 'organism' is a broader term encompassing species other than bacteria. For the purpose of distinctly claiming the subject matter, it is suggested that Applicant replace the limitation 'an organism' with the limitation --a bacterium--.

(v) Claims 19-57, which depend directly or indirectly from claim 18, are also rejected as

being indefinite because of the indefiniteness identified above in the base claim.

Rejection(s) under 35 U.S.C. 102

21) New claims 34-37, 46, 51 and 54 are rejected under 35 U.S.C. § 102(b) as being anticipated by Chong *et al.* (WO 99/42130, already of record).

The base claim 18 stands rejected as being anticipated by Chong *et al.* as explained above (see paragraph 16 *supra* and paragraph 15 of the Office Action mailed 01/07/04).

Chong's multivalent meningococcal capsular polysaccharide conjugate vaccine composition comprises an adjuvant, such as, aluminum hydroxide, aluminum phosphate, or Freund's adjuvant (see pages 32-34). Chong's immunogenic composition is prepared as a liquid solution or injectable (see page 31), and is contained in a kit (claim 35).

Claims 34-37, 46, 51 and 54 are anticipated by Chong *et al.*

Rejection(s) under 35 U.S.C. 103

22) Claims 18-33 and 51 are rejected under 35 U.S.C. § 103(a) as being unpatentable over McMaster (6,146,902 – Applicants' IDS submitted 07/07/04) in view of Andre *et al.* (*In: Modern Vaccinology.* (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, pp. 41-54, 1994, already of record), Levine *et al.* (*In: Abstracts of the Tenth International Pathogenic Neisseria Conference*, (Ed) Zollinger *et al.* Baltimore, USA, pages 228-230, November, 1997, already of record) and Lindberg AA (*Vaccine* 17: S28-S36, 1999 – Applicants' IDS).

It is noted that the transitional claim language 'comprises' within the recitation 'each of the conjugates comprises' in line 2 of the base claim 18, similar to the limitations, such as, 'having', 'including', 'containing', or 'characterized by', represents open-ended claim language and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ('comprising' leaves 'the claim open for the inclusion of unspecified ingredients even in major amounts').

McMaster disclosed a vaccine or immunological composition comprising a sterile liquid solution of individual capsular polysaccharide-protein conjugates comprising purified capsular polysaccharides of *Neisseria meningitidis* belonging to the serogroup A, C, W-135 and Y

conjugated to diphtheria toxoid protein for human or animal use (see column 7; Table 3; lines 59-64 of column 3; paragraph bridging columns 3 and 4; and lines 3-6 in column 4). The serogroup A, C, W-135 and Y meningococcal capsular polysaccharide conjugates are identified by their lot numbers as D01886, D01887, D01889 and D01880 respectively (see Table 3). The production of meningococcal serogroup A, C, Y and W-135 conjugates are described in columns 6 and 7; and Example 1. The meningococcal C glycoconjugate contained 0.33 mg of the polysaccharide conjugated to 1.89 mg of the carrier protein (see Table 2).

McMaster's disclosure differs from the instant invention in not expressly teaching a combination composition of two, three or four conjugates of the purified capsular polysaccharides of *Neisseria meningitidis* of serogroup A, C, W-135 and Y conjugated to diphtheria toxoid protein.

However, there was explicit suggestion in the art at the time of the invention to produce a cost-effective multivalent meningococcal A, C, Y and W-135 polysaccharide-protein conjugate vaccine. For instance, Levine *et al.* analyzed the cost-effectiveness of routine infant immunization with a quadrivalent meningococcal polysaccharide, A, C, Y and W-135-protein conjugate vaccine in the United States, and concluded that such an immunization with the quadrivalent meningococcal polysaccharide, A, C, Y and W-135-protein conjugate vaccine is likely to have a substantial impact on endemic meningococcal disease and may provide herd immunity (see pages 228-230, especially paragraph bridging pages 229 and 230). Levine *et al.* expressly called on vaccine manufacturers to provide such a conjugate vaccine that is cost-effective (see paragraph bridging pages 229 and 230).

Andre *et al.* taught that although a meningococcal vaccine comprising meningococcal serotypes B, C, Y and W-135 polysaccharides already exists which vaccine is immunogenic in children and adults, it is very poorly immunogenic in children less than 2 years old, an age when a vaccine would be most effective. Andre *et al.* taught that serotypes B, C, A, Y and W-135 are the most virulent and prevalent *N. meningitidis*. Andre *et al.* further expressly suggested that conjugate vaccines could be the answer to this problem. See first paragraph on page 45 of Andre *et al.* Andre *et al.* taught that the first developed group A and C meningococcal vaccines as well as the later developed Y and W-135 meningococcal vaccines though immunogenic in children and adults, are poorly immunogenic in children less than 2 years old, and that conjugate vaccines could be the answer to this problem. See first paragraph on page 45 of Andre *et al.*

Lindberg expressly taught that so far, all data indicate that meningococcal glycoconugate vaccines will have a great chance to be successful as the Hib and pneumococcal conjugates and that licensure is expected within the next coming years. Lindberg explicitly stated that meningococcal A + C + W135 + Y glycoconjugates will most likely be marketed (see thirds full paragraph in left column on page S34). Thus, Lindberg disclosed the reasonable expectation of success with a combination meningococcal A + C + W135 + Y glycoconjugate vaccine.

Given that individual purified meningococcal A, C, W-135 and Y capsular polysaccharide-diphtheria toxoid glycoconjugates were already known in the art at the time of the invention as taught by McMaster; given the art-recognized virulence and prevalence of serogroup C, A, Y and W-135 *N. meningitidis* as taught by Andre *et al.*; and given Levine's explicit calling on vaccine manufacturers to provide a cost-effective multivalent meningococcal polysaccharides-protein conjugate vaccine comprising conjugated meningococcal polysaccharides, A, C, Y and W-135, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine McMaster's vaccine composition comprising distinct protein-polysaccharide conjugates, i.e., a purified meningococcal serogroup A capsular polysaccharide-diphtheria toxoid conjugate; a purified meningococcal serogroup C capsular polysaccharide-diphtheria toxoid conjugate; a purified meningococcal serogroup Y capsular polysaccharide-diphtheria toxoid conjugate; and a purified meningococcal serogroup W-135 capsular polysaccharide-diphtheria toxoid, to produce the instant invention, with a reasonable expectation of success, because Levine *et al.* expressly taught that routine infant immunization with a quadrivalent meningococcal polysaccharide A, C, Y and W-135-protein conjugate vaccine is likely to have a substantial impact on endemic meningococcal disease and may provide herd immunity. Given Levine's express call for vaccine manufacturers to provide a meningococcal A, C, Y and W-135-protein conjugate vaccine that is cost-effective, one of skill in the art would have been motivated to produce the instant invention for the expected benefit of providing a cost-effective combination conjugate vaccine which is advantageously more effective and immunogenic even in children less than 2 years old including infants, who are at greatest risk of developing meningococcal disease against the most virulent and most prevalent *N. meningitidis* of serogroups B, C, A, Y and W-135 as taught by Andre *et al.*; and for the additional benefit of providing a multivalent meningococcal capsular

polysaccharide conjugate vaccine that is likely to have a substantial impact on endemic meningococcal disease and that may provide herd immunity as expressly taught by Levine *et al.* Such a combination vaccine would have had a reasonable expectation of success in terms of licensure and marketing as expressly taught by Lindberg.

Claims 18-33 and 51 are *prima facie* obvious over the prior art of record.

23) Claims 18-36, 46-51, 56 and 57 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992, already of record) and McMaster (6,146,902 – Applicants' IDS submitted 07/07/04) in view of Andre *et al.* (*In*: *Modern Vaccinology*. (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, pp. 41-54, 1994, already of record); Levine *et al.* (*In*: *Abstracts of the Tenth International Pathogenic Neisseria Conference*, (Ed) Zollinger *et al.* Baltimore, USA, pages 228-230, November, 1997, already of record) and Lindberg AA (*Vaccine* 17: S28-S36, 1999 – Applicants' IDS).

It is noted that the transitional claim language 'comprises' within the recitation 'each of the conjugates comprises' in line 2 of the base claim 18, similar to the limitations, such as, 'having', 'including', 'containing', or 'characterized by', represents open-ended claim language and therefore does not exclude additional, unrecited elements. See M.P.E.P 2111.03 [R-1]. See *Moleculon Research Corp. v. CBS, Inc., 793 F.2d 1261, 229 USPQ 805 (Fed. Cir. 1986)*; *In re Baxter, 656 F.2d 679, 686, 210 USPQ 795, 803 (CCPA 1981)*; *Ex parte Davis, 80 USPQ 448, 450 (Bd. App. 1948)* ('comprising' leaves 'the claim open for the inclusion of unspecified ingredients even in major amounts').

Costantino *et al.* taught a vaccine composition comprising two distinct protein-polysaccharide conjugates, wherein the first conjugate comprises a purified meningococcal serogroup A capsular polysaccharide conjugated to CRM 197 and a second conjugate comprises a purified meningococcal serogroup C capsular polysaccharide conjugated to CRM 197. The conjugate comprises an aluminum hydroxide adjuvant. The conjugate vaccine in phosphate buffer (i.e., liquid) is sterile-filtered. A 0.5 ml dose of the CRM 197-meningococcal A and C conjugate vaccine contains 11 microgram of each oligosaccharide and 88 micrograms of CRM 197. Costantino *et al.* first produced the individual serogroup A polysaccharide-CRM 197 and serogroup A polysaccharide-CRM 197 conjugates, and then produced the combined conjugate vaccine. See

'Materials and Methods'.

Costantino *et al.* differ from the instant invention in not teaching a vaccine composition comprising a protein-polysaccharide conjugate, wherein a conjugate comprises a purified meningococcal serogroup Y or W-135 capsular polysaccharide conjugated to a carrier protein.

However, a glycoconjugate composition comprising purified meningococcal serogroup Y and W-135 capsular polysaccharide-diphtheria toxoid protein conjugate was already known or available in the art at the time of the instant invention. For instance, McMaster disclosed a composition comprising a purified capsular polysaccharide of serogroup W-135 or Y *Neisseria meningitidis*, each linked to diphtheria toxoid protein for use as a medicament against meningitis (see claims 1, 6-8, 39 and 40; paragraph bridging pages 9 and 10; pages 10 and 12; and Examples 1, 2 and 4).

Furthermore, there was explicit suggestion in the art to produce a cost-effective multivalent meningococcal A, C, Y and W-135 polysaccharide-protein conjugate vaccine. For instance, Levine *et al.* analyzed the cost-effectiveness of routine infant immunization with a quadrivalent meningococcal polysaccharide, A, C, Y and W-135-protein conjugate vaccine in the United States, and concluded that such an immunization with the quadrivalent meningococcal polysaccharide, A, C, Y and W-135-protein conjugate vaccine is likely to have a substantial impact on endemic meningococcal disease and may provide herd immunity (see pages 228-230, especially paragraph bridging pages 229 and 230). Levine *et al.* expressly called on vaccine manufacturers to provide such a conjugate vaccine that is cost-effective (see paragraph bridging pages 229 and 230).

Additionally, Andre *et al.* taught that although a meningococcal vaccine comprising meningococcal serotypes B, C, Y and W-135 polysaccharides already exists which vaccine is immunogenic in children and adults, it is very poorly immunogenic in children less than 2 years old, an age when a vaccine would be most effective. Andre *et al.* taught that serotypes B, C, A, Y and W-135 are the most virulent and prevalent *N. meningitidis*. Andre *et al.* further expressly suggested that conjugate vaccines could be the answer to this problem. See first paragraph on page 45 of Andre *et al.* Andre *et al.* taught that the first developed group A and C meningococcal vaccines as well as the later developed Y and W-135 meningococcal vaccines though immunogenic in children and adults, are poorly immunogenic in children less than 2 years old, and that conjugate vaccines

could be the answer to this problem. See first paragraph on page 45 of Andre *et al.*

Lindberg expressly taught that so far, all data indicate that meningococcal glycoconjugate vaccines will have a great chance to be successful as the Hib and pneumococcal conjugates and that licensure is expected within the next coming years. Lindberg explicitly stated that meningococcal A + C + W135 + Y glycoconjugates will most likely be marketed (see thirds full paragraph in left column on page S34). Thus, Lindberg disclosed the reasonable expectation of success with a combination meningococcal A + C + W135 + Y glycoconjugate vaccine.

Given the art-recognized virulence and prevalence of serogroup C, A, Y and W-135 *N. meningitidis* as taught by Andre *et al.* and given the desirability in the art for a cost-effective multivalent meningococcal polysaccharides-protein conjugate vaccine comprising conjugated meningococcal polysaccharides, A, C, Y and W-135, as taught by Levine *et al.*, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to combine Costantino's vaccine composition comprising two distinct protein-polysaccharide conjugates, a purified meningococcal serogroup A capsular polysaccharide-CRM 197 conjugate and a purified meningococcal serogroup C capsular polysaccharide-CRM 197 conjugate with Chong's W-135- and Y polysaccharide-protein conjugates to produce the instant invention, with a reasonable expectation of success, because Andre *et al.* expressly suggested conjugate vaccines as the answer to the problem of poor immunogenicity, and Levine *et al.* expressly taught that routine infant immunization with a quadrivalent meningococcal polysaccharide A, C, Y and W-135-protein conjugate vaccine is likely to have a substantial impact on endemic meningococcal disease and may provide herd immunity. Given Levine's express call for vaccine manufacturers to provide a meningococcal A, C, Y and W-135-protein conjugate vaccine that is cost-effective, one of skill in the art would have been motivated to produce the instant invention for the expected benefit of providing a cost-effective combination conjugate vaccine which is advantageously more effective and immunogenic even in children less than 2 years old including infants who are at greatest risk of developing meningococcal disease as taught by Andre *et al.* and for the additional benefit of providing a multivalent meningococcal polysaccharide conjugate vaccine that is likely to have a substantial impact on endemic meningococcal disease and that may provide herd immunity as expressly taught by Levine *et al.* Such a combination vaccine would have had a reasonable

expectation of success in terms of licensure and marketing as expressly taught by Lindberg.

Claims 18-36, 46-51, 56 and 57 are *prima facie* obvious over the prior art of record.

24) Claim 37 is rejected under 35 U.S.C. § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992, already of record) and McMaster (6,146,902 - Applicants' IDS submitted 07/07/04) as modified by Andre *et al.* (*In*: *Modern Vaccinology*. (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, pp. 41-54, 1994, already of record); Levine *et al.* (*In*: *Abstracts of the Tenth International Pathogenic Neisseria Conference*, (Ed) Zollinger *et al.* Baltimore, USA, pages 228-230, November, 1997, already of record) and Lindberg AA (*Vaccine* 17: S28-S36, 1999 – Applicants' IDS) as applied to claims 35, 34 and 18 above, and further in view of Petre *et al.* (US 6,013,264).

The teachings of Costantino *et al.* and McMaster as modified by Andre *et al.*, Levine *et al.* and Lindberg are explained above, which do not disclose the aluminum adjuvant to be aluminum phosphate.

However, the use of aluminum phosphate adjuvant as an alternative adjuvant to aluminum hydroxide was well known, routine and conventional in the art at the time of the instant invention. For instance, Petre *et al.* taught the advantage of using aluminum phosphate in a vaccine composition. Petre *et al.* taught that aluminum phosphate, in soluble or gel form, serves as a conventional stabilizing agent in a vaccine composition in addition to serving as an adjuvant (see abstract; column 2, lines 19-23 and 46-62; column 5, lines 45-55).

Given the routine and conventional use of aluminum phosphate adjuvant with a conjugate vaccine, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to replace Costantino's aluminum hydroxide adjuvant with the art-known, alternate aluminum adjuvant, Petre's aluminum phosphate, in the Costantino's conjugate composition as modified by Andre *et al.*, Levine *et al.* and Lindberg to produce the instant invention with a reasonable expectation of success. Substitution of one aluminum adjuvant with another art-known interchangeable aluminum adjuvant for the same purpose would have been well within the realm of routine experimentation, would have been obvious to one of ordinary skill in the art, and would have brought about similar effects or results. Given Petre's disclosure that aluminum phosphate serves advantageously as a stabilizing agent in addition to serving as an adjuvant in a

vaccine composition, one of skill in the art would have been motivated to produce the instant invention for the expected benefit of stabilizing the prior art conjugate vaccine in addition to providing an adjuvant effect to the conjugate vaccine.

Claim 37 is *prima facie* obvious over the prior art of record.

25) Claims 38-45 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992, already of record) and McMaster (6,146,902 - Applicants' IDS submitted 07/07/04) as modified by Andre *et al.* (*In*: *Modern Vaccinology*. (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, pp. 41-54, 1994, already of record); Levine *et al.* (*In*: *Abstracts of the Tenth International Pathogenic Neisseria Conference*, (Ed) Zollinger *et al.* Baltimore, USA, pages 228-230, November, 1997, already of record) and Lindberg AA (*Vaccine* 17: S28-S36, 1999 – Applicants' IDS) as applied to claims 33 and 18 above, and further in view of Jennings *et al.* (US 5,811,102) ('102).

The teachings of Costantino *et al.* and McMaster as modified by Andre *et al.*, Levine *et al.* and Lindberg are explained above, which do not disclose the exact microgram range of polysaccharide(s) and carrier protein being present in their immunological composition.

However, it was well known and routine in the art at the time of the invention to vary the protein/polysaccharide ratio in a glycoconjugate. For instance, Jennings *et al.* ('102) expressly taught that variations in protein/polysaccharide ratio of a *Neisseria meningitidis* capsular oligosaccharide-protein glycoconjugate may be achieved by adjusting the ratio of the starting components in the conjugation reaction (see column 5, lines 54-57). Furthermore, with regard to the specific micrograms of the capsular polysaccharide(s) and the carrier protein recited in the instant claims, the process of optimizing, i.e., increasing or decreasing the micrograms of the capsular polysaccharide(s) and carrier protein to a desired amount or range in an art-known conjugate(s) is well within the realm of routine experimentation and would have been obvious to a skilled artisan at the time of the instant invention. It has been held legally obvious and within the routine skill in the art to optimize a result-effected variable. In the instant case, the microgram quantity of the capsular polysaccharide(s) and the carrier protein in the conjugate is clearly a result-effected variable, and it would have been *prima facie* obvious to vary or optimize the capsular polysaccharide and protein contents as desired in the prior art conjugate(s) by adjusting the ratio of

the starting components in the conjugation reaction as taught by Jennings *et al.* ('102), by routine experimentation, to produce the instant invention, with a reasonable expectation of success.

Claims 38-45 are *prima facie* obvious over the prior art of record.

26) Claims 52-55 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Costantino *et al.* (*Vaccine* 10: 691-698, 1992, already of record) and McMaster (6,146,902 - Applicants' IDS submitted 07/07/04) as modified by Andre *et al.* (*In*: *Modern Vaccinology*. (Ed) Kurstak *et al.* Plenum Medical Book Company, New York, pp. 41-54, 1994, already of record), Levine *et al.* (*In*: *Abstracts of the Tenth International Pathogenic Neisseria Conference*, (Ed) Zollinger *et al.* Baltimore, USA, pages 228-230, November, 1997, already of record) and Lindberg AA (*Vaccine* 17: S28-S36, 1999 – Applicants' IDS) as applied to claim 51, 33 and 18 above, and further in view of Avendano *et al.* (*Pediatric Infect. Dis J.* 12: 638-643, 1993).

The teachings of Costantino *et al.* and McMaster as modified by Andre *et al.*, Levine *et al.* and Lindberg are explained above, which do not disclose their immunological composition being contained in a single use syringe or a vial, or the syringe, or the vial being packaged in a box with instructions.

However, filling syringes or vials with an art known sterile vaccine composition and packaging the vaccine-filled syringes or the vials in a box along with instructions for vaccine administration was routine and conventional in the art at the time of the invention. For instance, Avendano *et al.* taught the routine use of a combined vaccine comprising a capsular polysaccharide-protein glycoconjugate in a single syringe (see title; abstract; Methods; and paragraph bridging left and right columns on page 639). Similarly, the safe storage or carriage of vaccines in vials has been a practice that is in routine use for decades in the art.

Given the routine and conventional use of single syringes to fill the conjugate vaccines in, as taught by Avendano *et al.* and the routine and conventional use of vials to safe store the vaccines for decades, it would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to use Avendano's syringes or art-known vaccine vials to store or hold Costantino's immunological composition as modified by McMaster, Andre *et al.*, Levine *et al.* and Lindberg, and package such vials or synringes in boxes along with proper instructions for use to produce the instant invention, with a reasonable expectation of success. One of skill in the art

would have been motivated to produce the instant invention for the expected benefit of safe storage; easy, safe and convenient transport of the prior art vaccine composition.

Claims 52-55 are *prima facie* obvious over the prior art of record.

Remarks

27) Claims 18-57 stand rejected.

28) Papers related to this application may be submitted to Group 1600, AU 1645 by facsimile transmission. Papers should be transmitted via the PTO Fax Center, which receives transmissions 24 hours a day and 7 days a week. The transmission of such papers by facsimile must conform with the notice published in the Official Gazette, 1096 OG 30, November 15, 1989. The RightFax number for submission of amendments, responses or papers is (703) 872-9306.

29) Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAG or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.Mov. Should you have questions on access to the Private PAA system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

30) Any inquiry concerning this communication or earlier communications from the Examiner should be directed to S. Devi, Ph.D., whose telephone number is (571) 272-0854. A message may be left on the Examiner's voice mail system. The Examiner can normally be reached on Monday to Friday from 7.15 a.m. to 4.15 p.m. except one day each bi-week, which would be disclosed on the Examiner's voice mail system.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's supervisor, Lynette Smith, can be reached on (571) 272-0864.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the Group receptionist whose telephone number is (571) 272-1600.

November, 2004

S. DEVI, PH.D.
PRIMARY EXAMINER